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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,523	02/15/2006	Jean-Louis Junien	111230104USWO	2929

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EXAMINER

KUDLA, JOSEPH S

ART UNIT	PAPER NUMBER
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1609

MAIL DATE	DELIVERY MODE
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07/25/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/568,523

Applicant(s)

JUNIEN ET AL.

Examiner

Joseph S. Kudla

Art Unit

1609

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 2/15/06, 9/26/06.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____.

DETAILED ACTION

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) TITLE OF THE INVENTION.
- (b) CROSS-REFERENCE TO RELATED APPLICATIONS.
- (c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
- (d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
- (e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
- (f) BACKGROUND OF THE INVENTION.
 - (1) Field of the Invention.
 - (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (g) BRIEF SUMMARY OF THE INVENTION.
- (h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
- (i) DETAILED DESCRIPTION OF THE INVENTION.
- (j) CLAIM OR CLAIMS (commencing on a separate sheet).
- (k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
- (l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Content of Specification

- (a) Title of the Invention: See 37 CFR 1.72(a) and MPEP § 606. The title of the invention should be placed at the top of the first page of the specification unless the title is provided in an application data sheet. The title of the invention should be brief but technically accurate and descriptive, preferably from two to seven words may not contain more than 500 characters.

- (b) Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11.
- (c) Statement Regarding Federally Sponsored Research and Development: See MPEP § 310.
- (d) The Names Of The Parties To A Joint Research Agreement: See 37 CFR 1.71(g).
- (e) Incorporation-By-Reference Of Material Submitted On a Compact Disc: The specification is required to include an incorporation-by-reference of electronic documents that are to become part of the permanent United States Patent and Trademark Office records in the file of a patent application. See 37 CFR 1.52(e) and MPEP § 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text were permitted as electronic documents on compact discs beginning on September 8, 2000.
- (f) Background of the Invention: See MPEP § 608.01(c). The specification should set forth the Background of the Invention in two parts:
 - (1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."
 - (2) Description of the Related Art including information disclosed under 37 CFR 1.97 and 37 CFR 1.98: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."
- (g) Brief Summary of the Invention: See MPEP § 608.01(d). A brief summary or general statement of the invention as set forth in 37 CFR 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the

Art Unit: 1609

invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

- (h) Brief Description of the Several Views of the Drawing(s): See MPEP § 608.01(f). A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.
- (i) Detailed Description of the Invention: See MPEP § 608.01(g). A description of the preferred embodiment(s) of the invention as required in 37 CFR 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.
- (j) Claim or Claims: See 37 CFR 1.75 and MPEP § 608.01(m). The claim or claims must commence on separate sheet or electronic page (37 CFR 1.52(b)(3)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps. See 37 CFR 1.75 and MPEP § 608.01(i)-(p).
- (k) Abstract of the Disclosure: See MPEP § 608.01(f). A brief narrative of the disclosure as a whole in a single paragraph of 150 words or less commencing on a separate sheet following the claims. In an international application which has entered the national stage (37 CFR 1.491(b)), the applicant need not submit an abstract commencing on a separate sheet if an abstract was published with the international application under PCT Article 21. The abstract that appears on the cover page of the pamphlet published by the International Bureau (IB) of the World Intellectual Property Organization (WIPO) is the abstract that will be used by the USPTO. See MPEP § 1893.03(e).
- (l) Sequence Listing. See 37 CFR 1.821-1.825 and MPEP §§ 2421-2431. The requirement for a sequence listing applies to all sequences disclosed in a given application, whether the sequences are claimed or not. See MPEP § 2421.02.

Art Unit: 1609

1. The disclosure is objected to because of the following informalities: The Specification as set forth is not in the proper order or format. Specifically, the Specification heading should appear in upper case, without underlining or bold type. In addition, section headings are out of order or missing. If a section heading from the above listed guidance is present and no text follows the section heading, the phrase "Not Applicable" should follow the section heading. Specifically, all section headings as enumerated above are missing.

2. A preliminary examination of this application reveals that it includes terminology which is so different from that which is generally accepted in the art to which this invention pertains that a proper search of the prior art cannot be made. For example: On page 9 lines 4-9, Applicant indicates the expression "therapeutically effective" is the capability of an agent to prevent, or reduce the severity of, the disorder being treated, ...and later in the following sentence that it is "understood to be equivalent to the expression "effective for the treatment, prevention and inhibition."

To prevent, as defined by Merriam-Webster Dictionary is to keep from happening or existing, which implies taking advance measures against something possible or probable. Furthermore, the definition of "to prevent" and the "act of preventing" embraces the complete 100% inhibition. Thus, the burden of enablement in the assertion of these statements are much higher than would be the case of enabling the treatment of the condition and is not achieved. As for the instant application in relation to the prior art, the prior art and instant application both enable the ability of metformin to decrease glycemic levels. That being stated, nowhere in the art or instant application

Art Unit: 1609

has the efficacy of metformin and a statin been enabled to prevent hyperglycemia in a subject. At best, within the limited rat models provided, the combination drug therapy exhibits the ability to decrease glucose levels. Since absolute success is not reasonably possible with most diseases/conditions, especially those having etiologies and pathophysiological manifestations as complex as a metabolic disorder such as diabetes, the specification, which lacks an objective showing that hyperglycemia can actually be prevented, is viewed as lacking an adequate written description of the same.

Applicant is required to provide a clarification of these matters or correlation with art-accepted terminology so that a proper comparison with the prior art can be made. Applicant should be careful not to introduce any new matter into the disclosure (i.e., matter which is not supported by the disclosure as originally filed).

3. The disclosure is objected to because of the following informalities: Applicant incorrectly to a patent number incorporated by reference on page 3 line 11. The patent number cannot be deduced from the supplied information.

4. The disclosure is objected to because of the following informalities: The statements found on page 8 lines 9-11, "The amount of metformin and the amount of statin together provide a dosage or amount of the combination that is sufficient to constitute an effective amount of the combination," and on page 1, lines 20-23, "High levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (apo-B, a component of a membrane complex for LDL-C) promote human atherosclerosis, and decreased levels of HDL-C and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis," are unclear.

Art Unit: 1609

5. The use of the trademarks for MEVACOR (page 3, line 19), LESCOL (page 4, line 3), LIPITOR (page 4, line 22), ZOCOR (page 5, line 14), BAYCOL (page 5, line 31), PRAVACHOL (page 6, line 18) and CRESTOR (page 6, line 31) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The use of the terminology or "therapeutically effective" with the term "controlling" is contentious.

Applicant asserts in claim 1 a "method for controlling... glycemia...(with) a therapeutically effective dose." As defined by *The American Heritage® Dictionary of the English Language, Fourth Edition*, the word control can mean to direct or regulate.

Art Unit: 1609

Control, in the broadest meaning of the word, means complete control. As stated above, applicants' definition of the phrase "therapeutically effective" with the word to "control" implies the ability to direct/ control completely to the prevention of elevated glucose levels. To prevent, as defined by Merriam-Webster Dictionary is to keep from happening or existing, which implies taking advance measures against something possible or probable. Furthermore, the definition of "to prevent" and the "act of preventing" embraces the complete 100% inhibition. Thus, the burden of enablement in the assertion of this claim is much higher than would be the case of enabling the treatment of the condition and is not achieved. As for the instant application in relation to the prior art, the prior art and instant application both enable glucose level reduction when the combination of metformin and a statin are administered. That being stated, nowhere in the art or instant application has the efficacy of the combination of metformin and a statin been enabled to prevent or completely control the occurrence of elevated glucose levels. Since absolute success is not reasonably possible with most diseases/conditions, especially those having etiologies and pathophysiological manifestations as complex as a metabolic disorder such as diabetes, the specification, which lacks an objective showing that elevated glucose levels can actually be prevented or completely controlled, is viewed as lacking an adequate written description of the same. In conclusion, applicant is enabled for the treatment of elevated glucose levels of a Type II diabetic subject with a combination of metformin and a statin.

Appropriate correction is required

The following is a quotation of the second paragraph of 35 U.S.C. 112:

Art Unit: 1609

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 3-5, 8-11 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The indication of the group or subject to be treated and the indication for which treatment is given is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the claim. As an example, Claim 1 could be remedied by the addition of a subject or group to which the invention could be administered along with a statement that the therapy is given to decrease hyperglycemia or treat diabetes. Currently, the instant claim 1 reads on anyone, without regard to whether the subject has diabetes.

8. Claim 1 recites the limitation "the co-administration." There is insufficient antecedent basis for this limitation in the claim.

9. Claims 3, 4, 5, 11 and 13 recite the limitation "the form." There is insufficient antecedent basis for this limitation in the claim.

10. Claims 2, 3, 4, 5, 9 and 10 recite the limitation "the group." There is insufficient antecedent basis for this limitation in the claim.

11. Claims 3 and 4 recite the limitation "the hydrochloride." There is insufficient antecedent basis for this limitation in the claim.

12. Claim 5 recites the limitation "the sodium ion." There is insufficient antecedent basis for this limitation in the claim.

13. Claim 8 recites the limitation "the weight ratio." There is insufficient antecedent basis for this limitation in the claim.

Art Unit: 1609

14. Claims 9 and 10 recite the limitation "the active components." There is insufficient antecedent basis for this limitation in the claim.

15. Claim 13 recites the limitation "the two active components." There is insufficient antecedent basis for this limitation in the claim.

Appropriate correction is required

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-9 and 11-13 are rejected under 35 U.S.C. 102(b) as being clearly anticipate by Freese et al. (US 2003/0171407).

The claims are drawn towards a solid-oral pharmaceutical composition that contains a statin and metformin in a defined ratio and delivery range that can also exist as an extended release product.

Freese et al teaches (paragraph 50) a novel ~~composition of a~~ HMG-CoA reductase inhibitor (statin) and metformin within the ~~same~~ pharmaceutical composition. Within the same paragraph, the form in which metformin exists is as metformin hydrochloride. Freese et al. also teaches (paragraph 19) that the "pharmaceutical agents presently known in the HMG-CoA reductase inhibitor group can include the statin drugs. Presently known statin drugs include simvastatin, atorvastatin calcium, fluvastatin sodium, lovastatin, pravastatin sodium, and rosuvastatin calcium. HMG-CoA

Art Unit: 1609

reductase inhibitor drugs are presently marketed under the trade names ZOCOR TM (simvastatin), LIPITOR TM (atorvastatin calcium), LESCOL TM (fluvastatin sodium)."

The accepted guidelines as quoted from the Physician's Desk Reference for statin therapy in Freese et al is noted in paragraph 49 and encompasses the ranges as quoted herein, "the recommended daily dosage range for simvastatin is in the range 5-80 milligrams/day; for atorvastatin calcium, 10-80 milligrams/day; for fluvastatin sodium, 20-80 milligrams/day; for lovastatin, 10-80 milligrams/day; and for pravastatin sodium, 10-40 milligrams/day. Dosage guidelines for rosuvastatin calcium are expected to be in the range 5-80 milligrams/day." The accepted guidelines as quoted from the Physician's Desk Reference for metformin therapy in Freese et al. is noted in paragraph 70 and encompasses the ranges as quoted herein, the recommended daily dosage range for metformin hydrochloride is in the range 1500-2550 milligrams/day." Although the ranges listed in Freese et al do not encompass the ranges in the instant claim set in their entirety, this type of modification would have been well within the purview of the skilled artisan and no more than an effort to optimize results. Freese et al also teaches solid-oral delivery of the composition in a capsule (paragraph 58) or tablet (paragraph 59) form. An embodiment of the invention of Freese et al is a sustained-release formulation (extended-release composition) (paragraph 51).

17. Claims 1-9, 12 and 14 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Alsheikh-Ali et al ("Risk of Adverse Events With Concomitant Use of Atorvastatin or Simvastatin and Glucose- Lowering Drugs (Thiazolidinediones,

Art Unit: 1609

Metformin, Sulfonylurea, Insulin and Acarbose) " The American Journal of Cardiology, Vol 89 June 1, 2002. pp. 1308-1310).

The claims are drawn towards the co-administration of a statin drug product with a metformin drug product simultaneously.

Alsheikh et al. clearly teaches the administration of metformin and a statin (see table 1, pg. 1309, heading) wherein it is stated "Percentage of Patients With an Adverse Event While Taking Either Simvastatin or Atorvastatin Who Were Also Taking on Antidiabetic Medication." Within the table, metformin is indicated as one of the antidiabetic medications.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Art Unit: 1609

18. Claims 1-8, 10-11 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freese et al. (US 2003/0171407) in view of Mutschler et al (Drug Actions, 1995).

Freese et al teaches (paragraph 50) a novel composition of a HMG-CoA reductase inhibitor (statin) and metformin within the same solid-oral pharmaceutical composition. However, Freese et al does not teach the pharmaceutical composition as a solution, suspension or emulsion.

Mutschler et al. teaches (pp. 6-8) that the parenteral route of administration of a pharmaceutical composition has certain advantages over other modes of administration. Intravenous drug delivery of a solution as an administration route would have the benefit of exact dosing, avoidance of the GI tract, wider range of pH in delivery, rapid administration, etc... Therefore, it would have been obvious to one of ordinary skill in the art at the time the application was filed to combine the teachings of the above references (Freese et al and Okuma et al) to arrive at an intravenous injection of a solution as an administration route.

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph S. Kudla whose telephone number is (571) 270-3288. The examiner can normally be reached on 9am-5pm EST.

Art Unit: 1609

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JK

A handwritten signature in black ink, appearing to read 'M. Meller', with a long horizontal flourish extending to the right.

MICHAEL MELLER
PRIMARY EXAMINER